British Journal of Rheumatology 1996;**35**:867–873

DISEASE ACTIVITY IN ANKYLOSING SPONDYLITIS: SELECTION OF A CORE SET OF VARIABLES AND A FIRST STEP IN THE DEVELOPMENT OF A DISEASE ACTIVITY SCORE

M. C. W. CREEMERS, M. A. VAN 'T HOF,* M. J. A. M. FRANSSEN,† L. B. A. VAN DE PUTTE, F. W. J. GRIBNAU‡ and P. L. C. M. VAN RIEL

*Department of Rheumatology, University Hospital Nijmegen, St Radboud, PO Box 9101, 6500 HB Nijmegen, *Department of Medical Statistics, Catholic University Nijmegen, †Department of Rheumatology, St Maartens Hospital, Nijmegen and ‡Department of Clinical Pharmacology, University Hospital Nijmegen, Nijmegen, The Netherlands*

SUMMARY

A large number of variables are available for the assessment of disease activity in ankylosing spondylitis (AS). The aim of this study was to evaluate the validity of commonly used variables, to select a core set of valid variables for disease activity and finally to compute an AS disease activity score (AS-DAS). Data from two longitudinal studies were used. Principal component analysis and reliability analysis resulted in 11 factors: cervical mobility, lumbar flexion, subjective complaints, functional index (FI), enthesis index (EI), inflammatory response, IgA, IgM, root joints, swollen joints and spinal mobility. Based on discriminating power, reproducibility and correlation with disease duration, seven single variables were selected. In a subsequent discriminant analysis, an AS-DAS was computed of five variables, i.e. subjective complaints, FI, EI, root joints and C-reactive protein, which should be validated in the future. A core set of process variables solves the problem of multiple testing in clinical trials, and improves comparability.

KEY WORDS: Disease activity, Ankylosing spondylitis, Outcome, Validity.

THE evaluation of disease activity in ankylosing spondylitis (AS) is a complex and multifactorial problem. Therefore, a large number of different variables are being used for the evaluation of patients with this disease. Guidelines of the ARA [1] and European League Against Rheumatism (EULAR) [2] for clinical trials in AS have been developed. However, the validity, reproducibility and the mutual relationship of this large number of variables have not been studied [3, 4], with the exception of some variables [5]. Laboratory variables, e.g. C-reactive protein (CRP), ESR and IgA, are not abnormal in every patient with active disease [6–14], and primarily appear to be associated with peripheral arthritis [15, 16] and extra-articular features [17]. Another major problem is the lack of sensitivity to change, especially in those variables measuring spinal mobility [2], possibly caused by the fact that commonly used variables are a combination of momentary disease activity, i.e. process of the disease, and of the result, i.e. outcome of the disease. As a result of these problems, a wide variety of variables are used in clinical trials on AS, making comparison between different studies difficult.

The aim of this study was to evaluate the validity of commonly used variables for the assessment of disease activity in AS. Data from two clinical longitudinal prospective studies, in which patients had to have a high active disease upon study entry, were used. The results of this evaluation bring within reach the selection of a core set of variables which are reliable, reproducible and sensitive to change. Finally, this might lead to the development of a disease activity score for AS.

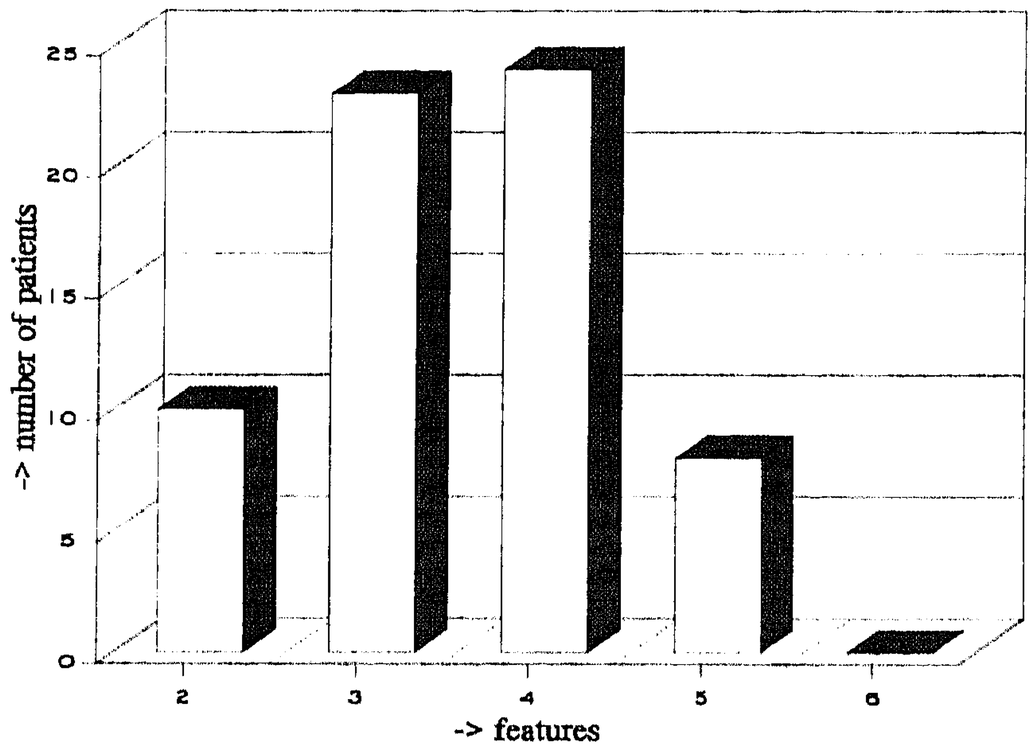
Submitted 7 July 1995; revised version accepted 4 March 1996.

Correspondence to: M. Creemers, Department of Rheumatology, University Hospital Nijmegen, St Radboud, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

PATIENTS AND METHODS

Patients

Records of AS patients participating in two prospective longitudinal studies were used. Patients of either sex, aged between 18 and 60 yr, had to fulfil the modified New York criteria [18]. Patients participated either in a 48 week double-blind NSAID study ($n = 59$), entering after a washout period for NSAIDs, or a 24 week open study with methotrexate (MTX), in which patients had to have failure of treatment with NSAIDs and sulphasalazine (SASP) [19]. In both studies, patients had to have active disease, defined as a clear need for anti-inflammatory, analgesic drug. In addition, they had to have at least two of the following features: (1) spinal pain, (2) morning stiffness of at least 30 min; (3) chest pain; (4) pain in both buttocks; (5) peripheral arthritis; (6) raised ESR $\geqslant$ 30 mm/1st h or CRP $\geqslant$ 20 mg/l or IgA $\geqslant$ 3.9 mg/l. Three patients participated first in the NSAID study and subsequently in the MTX study, only data from the MTX study of these patients were considered. Two other patients were retrospectively excluded from the NSAID study because they did not meet the above-described criteria for active disease. In total, there were 65 patients (48 men, 17 female); 62 of them were HLA-B27 positive, six had peripheral arthritis and four iridocyclitis. Mean age was 38 yr (S.D. = 9), mean disease duration 9 yr (S.D. = 8). Features present at study entry are shown in Table I. In Fig. 1, the number of patients and the



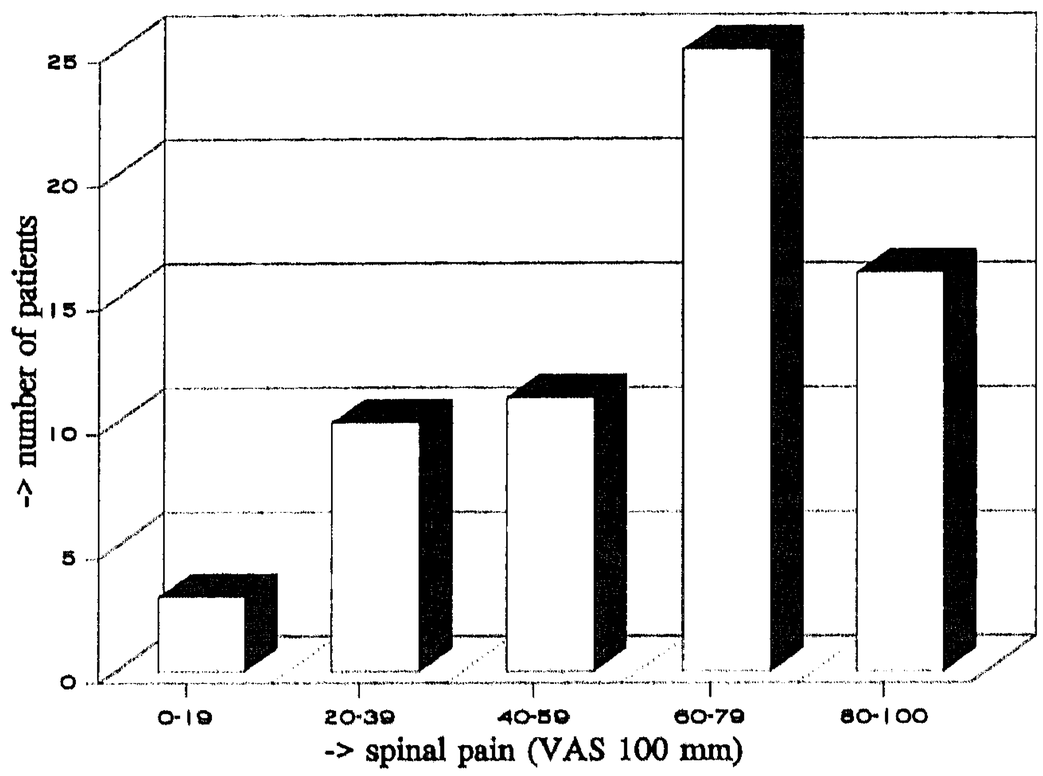


FIG. 1.—Numbers of features present for active disease in 65 patients.

numbers of features present for active disease are shown. Figure 2 shows the division of patients and the degree of pain and stiffness.

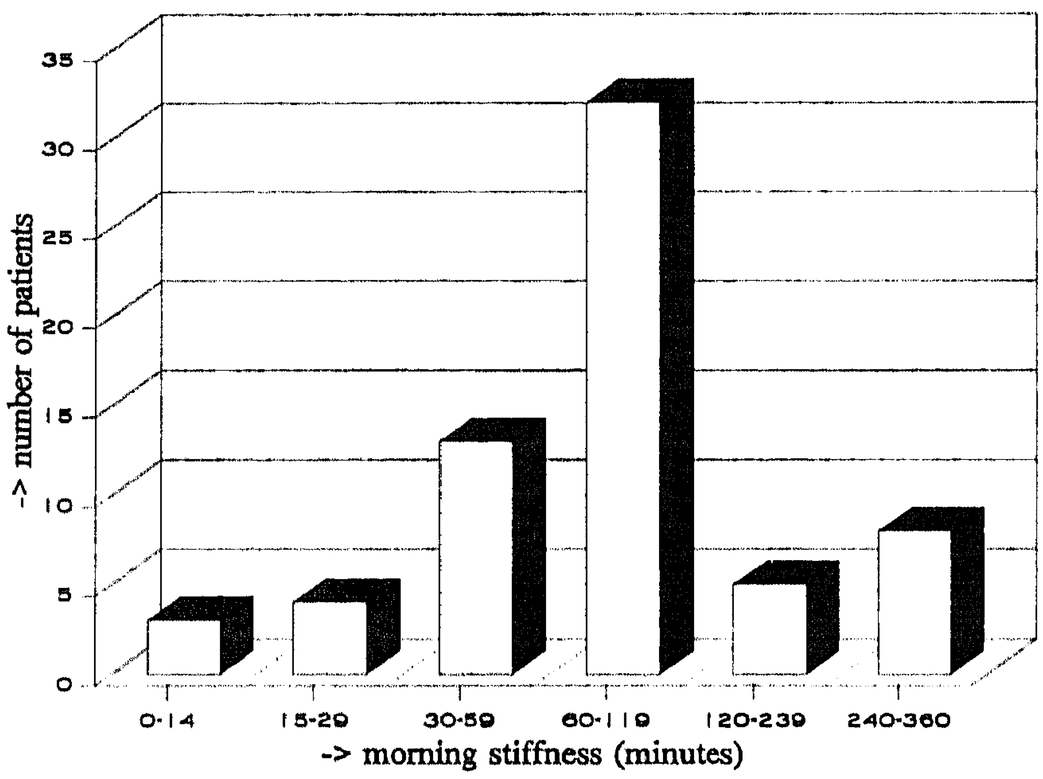


FIG. 2.—Division of the degree of pain and morning stiffness.

Measurements

For measurement of disease activity, the following variables were assessed at every visit.

Clinical variables. Occiput-to-wall distance, measured in centimetres with the patient standing as erect as possible with heels and back against the wall; chest expansion: the difference in centimetres between the circumference of the chest at nipple line on full inspiration and full expiration; Schober 10 cm index [20]; modified Schober 15 cm index [5]; lumbar flexion index [21]; fingertip-to-floor distance: the distance in centimetres between the third finger and the floor with the patient bending forward maximally, without flexing the knees; lumbar lateral flexion [22], as a percentage of body height; the number of swollen joints; enthesis index [23], maximal score being 90; root joint index: pain of shoulders and hips on palpation and/or passive movement was assessed with pain graded from 0 to 3 and the sum of the scores being the index; mobility of the cervical spine (in degrees): rotation using a goniometer, and lateral flexion, anteflexion and retroflexion using a hydrogoniometer.

Subjective variables. Spinal pain during the day, spinal pain during the night and general wellbeing were assessed by using a 100 mm visual analogue scale (VAS); duration of morning stiffness after rising, recorded in minutes with a maximum of 360 min.

TABLE I
Features of active disease present at study entry of all 65 patients

Feature	Number of patients
Spinal pain	62
Morning stiffness ≥30 min	59
Chest pain	29
Buttock pain	24
Raised ESR/IgA/CRP*	48

*ESR ≥ 30 mm or CR ≥ 20 mg/l or IgA ≥ 3.9 mg/l.

Laboratory variables. ESR, C-reactive protein, complete blood cell count, IgA, G and M.

Functional assessment. A Dutch functional index for AS [24], in essence a modification of the functional index of Dougados *et al*. [25, 26] was completed at week 0 and every 12 weeks. The maximum score was four.

Variables which have been measured on both sides, i.e. lumbar lateral flexion, cervical rotation and cervical lateral flexion, were reported as a good and bad score for each patient irrespective of the side.

Definition of disease activity and selection of records

Patients were seen 12 times in the NSAID study and eight times in the MTX study. This resulted in 736 records for these 65 patients. Patients' records were selected guided by the definitions of high and low disease activity. Disease activity was defined as low in the NSAID study if patients had used a stable dose of NSAIDs for at least 24 weeks, and in the MTX study if patients continued MTX after 24 weeks. Disease activity was defined as high at week 0 of both studies;

TABLE II
Median and percentiles 10 and 90 of assessed variables (101 records)

Variable	p10	Median	p90	Skewness	Skewness after transformation
Spinal pain at night (VAS)	6	37	82	0.19	–
Spinal pain during the day (VAS)	6	46	82	0.04	–
General wellbeing (VAS)	10	46	84	0.14	–
Morning stiffness (minutes)	0	60	144	2.34	0.08 (sqrt)
Fingertip-to-floor distance (cm)	0	16	41	0.62	–
Lumbar flexion index (cm)	17.0	20.0	22.0	−0.40	–
Modified Schober index (cm)	17.0	20.0	21.5	−0.25	–
Schober 10 cm index (cm)	11.0	14.0	15.0	−0.37	–
Lateral flexion good side (%)	1.75	4.17	9.38	0.83	–
Lateral flexion bad side (%)	2.20	5.14	10.17	0.69	–
Occiput-to-wall distance (cm)	0	1	10	1.75	0.62 (sqrt)
Chest expansion (cm)	2.0	3.5	6.0	1.02	−0.76 (ln)
Cervical mobility (degrees)					
Anteflexion	16	52	71	−0.30	–
Retroflexion	20	42	68	0.11	–
Lateral flexion good side	13	32	48	0.05	–
Lateral flexion bad side	14	40	58	−0.04	–
Rotation good side	30	62	80	−0.69	–
Rotation bad side	40	70	84	−1.08	–
Enthesis index	0	7	29	1.97	0.34 (sqrt)
Root joint index	0	0	2	3.28	1.29 (d-sqrt)
Dutch functional index	0.24	1.12	2.17	0.20	–
Number of swollen joints	0	0	1	5.40	2.26 (d-sqrt)
ESR (mm/1st h)	6	15	53	1.92	−0.09 (ln)
C-reactive protein (mg/l)	4	19	51	3.61	−0.20 (ln)
Platelets (10^9/l)	217	274	405	1.53	0.26 (ln)
IgA (mg/l)	1.61	2.74	5.15	0.77	–
IgG (mg/l)	8.50	11.28	17.60	3.19	1.04 (ln)
IgM (mg/l)	0.80	1.74	2.74	0.72	–

VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; ln, logarithmic transformation; sqrt, square root transformation; d-sqrt, double square root transformation.

however, records of 10 patients at week 0 were incomplete due to missing variables. Finally, 101 records were selected for further analysis: 46 records with a low disease activity and 55 with a high disease activity. For 36 patients, both a low and a high disease activity record was available. Ranges of variables of these 101 records are shown in Table II.

Statistical analysis

Variables used in multivariate statistical analysis have to be normally distributed. If necessary, assessed variables were, therefore, transformed to obtain normality. To find subgroups of variables, principal component analysis was performed on all variables. For reliability testing, Cronbach's α [26] (as a measure of consistency) was calculated for the factors. A forward stepwise discriminant analysis was performed for the determination of factors discriminating significantly between a high and a low disease activity. Because the number of visits in the two studies was different, resulting in different numbers of records per patient, only the selected 101 patients' records were used for factor analysis and discriminant analysis.

Records of patients for whom both a high and low disease activity record were available were analysed using paired *t*-tests. Of these paired observations, the discriminating power was expressed as the standardized difference (difference/pooled S.D.).

All records of the 59 patients of the NSAID study were used for analysis of the reproducibility of variables, calculated with an interperiod correlation matrix and the corresponding regression line was calculated for the estimation of measurement–remeasurement correlation (r_0) [27]. Because variables might be a combination of process and outcome of the disease, the relationship with disease duration was analysed. For this, Spearman rank correlations were computed of disease duration and all assessed variables of weeks 0 and 12 of the NSAID study. In order to separate process and possible outcome variables, those variables having a significant correlation with disease duration were considered mainly assessing outcome.

Finally, a set of process variables was then selected and an index for disease activity calculated using discriminant analysis.

RESULTS

Factor analysis and reliability

Principal component analysis was performed on 27 variables of the 101 selected records. Seven factors were found with eigenvalues larger than one and a cumulative explained variance of 76%.

Cronbach's α was calculated for the composed factors. Factors in which variables within a factor did not give a positive contribution to the reliability were subsequently split into separate factors. Cronbach's α

TABLE III
Factors out of principal component analysis and reliability analysis

Assessor	Patient	Laboratory
1. 'Cervical mobility' Cervical anteflexion Cervical retroflexion Cervical rotation g Cervical rotation b Cervical lateral flexion g Cervical lateral flexion b	7. 'Subjective complaints' Spinal pain day Spinal pain night General wellbeing Morning stiffness	9. 'Inflammatory response' ESR CRP IgG Platelets
2. 'Lumbar flexion' Modified Schober Lumbar flexion index Schober 10 cm index	8. Functional index	10. IgA
3. Enthesis index		11. IgM
4. Root joints		
5. Swollen joints		
6. 'Spinal mobility' Fingertip-to-floor distance Occiput-to-wall distance Lumbar lateral flexion g Lumbar lateral flexion b		

g, good side; b, bad side.

of all composed factors varied from 0.82 to 0.97 and may be considered as reliable. Finally, there were 11 factors: cervical mobility (Factor 1), lumbar flexion (Factor 2), the enthesis index (Factor 3), the root joints (Factor 4), swollen joints (Factor 5), 'spinal mobility' (Factor 6), 'subjective complaints' (Factor 7), the functional index (Factor 8), 'inflammatory response' (Factor 9), IgA (Factor 10) and IgM (Factor 11) (see Table III).

Variables were scaled, and scaling factors were chosen to equalize the S.D. of variables within each factor. Factor values then were calculated as the mean of the variables corresponding with the factor.

Discriminant analysis

Paired *t*-testing was performed on the factor values of the records of 36 patients with observations both with a high and low disease activity. For further analysis, Factor 1 was excluded because no significant change was found ($P = 0.16$). The number of swollen joints also showed no significant change ($P = 0.06$); as this was possibly due to the small number of patients with peripheral arthritis, we did not exclude this factor.

The stepwise forward discriminant analysis showed five significant steps entering: 'subjective complaints' (Factor 7), 'inflammatory response' (Factor 9), root joints (Factor 4), enthesis index (Factor 3) and IgA (Factor 10). Table IV shows the relative importance of factors and variables used in the discriminant analysis. Canonical correlation was 0.64 and 80% were correctly classified.

The discriminating power, computed as the standardized differences from paired *t*-testing of the 36 patients, and the correlations with the discriminant score (101 records) gave similar information about the factors used in the analyses (see Table IV).

Disease duration

Variables and factor values from the NSAID study of weeks 0 and 12 and corresponding differences were used for the calculation of Spearman rank correlations with disease duration. Only statistically significant correlations are shown in Table V.

Reproducibility

In longitudinal studies, the quality of variables can be determined by the calculation of interperiod correlations. These intercorrelations can be plotted against time interval and a regression line can be calculated. The intersection of this line with the vertical axis (intercept) is an estimation of the direct measurement–remeasurement correlation (r_0) and this

TABLE IV
Correlations of 11 factors with discriminant score and discriminating power

Factor	Correlations with discriminant score (101 records)†	Standardized difference (72 paired records)‡
Subjective complaints* (F 7)	0.84	1.17
Enthesis index* (F 3)	0.63	0.89
Functional index (F 8)	0.56	0.69
Spinal mobility (F 6)	−0.42	0.46
Root joints* (F 4)	0.38	0.50
Lumbar flexion (F 2)	0.30	0.44
Inflammatory response* (F 9)	−0.24	0.33
IgM (F 11)	0.17	0.40
Swollen joints (F 5)	0.12	0.34
IgA* (F 10)	0.10	0.25
Cervical mobility (F 1)		0.16

F, factor (see Table III).
*Factors selected stepwise in discriminant analysis.
†65 patients.
‡36 patients.

TABLE V
Analyses used for selection of variables

Factors and variables	Selected for AS-DAS	Discriminating power standardized difference ($n = 36$)	Reproducibility estimated r_0 ($n = 59$)	Correlations with disease duration	
				week 0	week 12
'Cervical mobility'		0.16			
Anteflexion	–	0.11	0.77		– 0.32*
Retroflexion	–	0.01	0.81		
rotation g	–	0.29*	0.82		
rotation b	–	0.29*	0.80		
lateral flexion g	–	0.06	0.87		
lateral flexion b	–	0.05	0.86		
'Lumbar flexion'		0.44***			
Lumbar flexion index	(X)	0.63****	0.88		
Modified Schober index	–	0.30****	0.87		
Schober 10 cm index	–	0.35***	0.85		
'Subjective complaints'		1.17****			
Spinal pain during the day	X	1.06****	0.65		
Spinal pain at night	–	0.83****	0.63		
General wellbeing	–	1.11****	0.58		
Morning stiffness	–	0.75****	0.55		
Enthesis index	X	0.89****	0.74		
Functional index	X	0.69****	0.92		
'Inflammatory response'		0.33****			
ESR	–	0.17	0.87		
CRP	X	0.72	0.74		
IgG	–	0.23	0.86		
Platelets	–	0.02	0.85		
IgA	–	0.25***	0.94		
IgM	–	0.40****	0.95		– 0.28*
Root joints	X	0.50*	0.67		
Swollen joints	(X)	0.34$^{p=0.06}$	0.80		
'Spinal mobility'		0.46****		– 0.30*	– 0.37****
Fingertip-to-floor distance	–	0.44****	0.94		
Occiput-to-wall distance	–	0.31***	0.89	0.27*	0.27*
Lumbar lateral flexion g	–	0.31****	0.94		– 0.33**
Lumbar lateral flexion b	–	0.31****	0.94	– 0.27*	– 0.35****
Chest expansion	–	0.34***	0.86		

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; b, bad side; g, good side.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.005$; ****$P < 0.001$.
X = selected variable.

may be interpreted as a quality measure of a variable [28]. Estimated r_0 of variables belonging to composed factors are shown in Table V.

Selection of a core set of variables

The selection of useful process variables is based on discriminating power (standardized difference), reproducibility and a lack of correlation with disease duration. Factors and variables correlating with disease duration were considered assessing primarily outcome and not selected. For reasons of simplicity and practicality, only one single variable out of a composed factor was selected. The selection of factors and variables was based on the largest discriminating power (standardized difference) and reproducibility (measurement–remeasurement correlation, r_0). Variables with standardized differences of <0.30 were not taken into account. Selected process variables are thus (marked in Table V): (1) spinal pain during the day (VAS); (2) lumbar flexion index; (3) root joints; (4) enthesis index; (5) swollen joints; (6) functional index; (7) CRP.

Composition of a disease activity score

A forward stepwise discriminant analysis on the seven selected process variables resulted in a correlation with a discriminant score of 0.07 for swollen joints (Factor 5), while the remaining six variables had correlations of at least 0.35. Therefore, this variable was left out of consideration. The subsequent discriminant analysis showed a positive coefficient for the lumbar flexion index and a negative correlation with the discriminant score. Because of this discrepancy, this variable was considered as being unstable, i.e. its discriminating power is completely expressed by the other (interrelated) variables. Finally, the ankylosing spondylitis disease activity score (AS-DAS) was computed with a discriminant analysis using assessor, patient and laboratory variables (in total five), namely spinal pain during the day (VAS),

TABLE VI
Computation of the ankylosing spondylitis disease activity score (AS-DAS), medians and percentiles 10 and 90 of the five selected variables

	Correlation with discriminant score	Coefficient	High disease activity* ($n = 55$)‡			Low disease activity* ($n = 46$)‡		
			P_{10}	P_{50}	P_{90}	P_{10}	P_{50}	P_{90}
Functional index	0.69	0.238	0.50	1.41	2.18	0.02	0.62	1.76
Enthesis index (sqrt)†	0.58	0.113	0	16	36	0	2	22
Spinal pain during the day	0.51	0.318	26	62	86	3	23	70
CRP (ln)†	0.43	6.540	7	24	75	3	12	35
Root joints (d-sqrt)†	0.35	5.245	0	0	2	0	0	1
Computed AS-DAS			30.9	44.7	60.6	13.3	26.8	40.0

Computation: AS-DAS = 0.238 × (functional index) + 1.13 × sqrt (enthesis index) + 0.318 × (spinal pain) + 6.54 × ln (CRP) + 5.245 × d-sqrt (root joints).
*Percentiles.
†Transformation: ln = logarithmic; sqrt = square root; d-sqrt = double square root.
‡Number of records.

enthesis index, functional index, root joints and CRP. Three variables had to be transformed to obtain normality for this analysis. Correlations with the final score, means and S.D. of the separate variables and coefficients for the final formula are shown in Table VI. The canonical correlation was 0.67 and 82% were correctly classified in this final discriminant analysis.

DISCUSSION

Judgement of disease activity in rheumatic diseases is a complex process and forms the basis of clinical decisions. Assessed variables are often a combination of process and outcome of the disease. In AS, commonly used variables contain a lot of interpretation problems, as stated in the Introduction. In the past, some indices of disease activity in AS have been proposed, based on clinical judgement [29–33]. However, the majority of these indices have not been validated. Recently, Salaffi *et al.* [34] analysed data on 45 AS patients in order to identify groups of variables out of the large number available. Three groups of variables were identified, measuring disease activity, damage and functional status, the latter being a combination of disease activity and disease outcome.

In our study longitudinal data on AS patients were analysed to identify those variables which discriminate for disease activity. Since no 'gold standard' for disease activity in AS is available, pre-defined criteria for high and low disease activity were used. Two groups of patients' records were formed: one group with high and one group with low disease activity. For evaluation of reproducibility, discriminating power and the correlation of variables and factors with disease duration, a pre-defined analysis strategy [35], including principal component analysis to form subgroups of reliable, interrelated variables, reliability of factors was used. This evaluation resulted in a selection of seven process variables. Finally, a disease activity score was computed of five variables, derived from a discrimant analysis.

The core set of seven process variables encompassed the lumbar flexion index, spinal pain during the day, enthesis index, functional index, CRP, root joints and the number of swollen joints, comprising assessor and laboratory variables as well as patient variables. In a discriminant score for the construction of a disease activity score, two variables had to be excluded: (a) 'swollen joints' because of a low correlation with the discriminant score and (b) 'the lumbar flexion index', which appeared to be an unstable variable, i.e. its discriminating power is completely expressed by the other (interrelated) variables. It is striking that pain assessed in three of these variables, in 2, gives most weight to the AS-DAS.

In conclusion, the proposed AS-DAS should be validated further. For standardization purposes, the selected core set of process variables should be used in future clinical trials in AS, resulting in improvement of the comparability of different studies. Additionally, the problem of multiple statistical testing will be solved since only a reduced number of variables, and eventually a single composed variable, i.e. the AS-DAS, have to be analysed for the evaluation of disease activity.

ACKNOWLEDGEMENT

This study was supported by a grant from S. A. Nycomed Christiaens B.V., Belgium.

REFERENCES

1. *Guidelines for the clinical evaluation of anti-inflammatory and anti-rheumatic drugs (adults and children)*. US Department of Health and Human Services, Public Health Service, Food and Drug Administration, April 1988, pp. 38–40.
2. *Guidelines for the clinical investigation of drugs used in rheumatic diseases, European drug guideline series 5*. World Health Organization, Regional office for Europe, Copenhagen, European League Against Rheumatism, March 1985, p. 12.
3. Laurent MR, Buchanan WW, Bellamy N. Methods of assessment used in ankylosing spondylitis clinical trials: a review. *Br J Rheumatol* 1991;**30**:326–9.
4. Rigby AS, Silman AJ. Outcome assessment in clinical trials of ankylosing spondylitis. *Br J Rheumatol* 1991;**30**:321–5.
5. Moll JMH, Wright V. Normal range of spinal mobility. *Ann Rheum Dis* 1971;**30**:381–6.
6. Espinoza LR, Gaylord SW, Bocanegra TS, Vasey FB, Germain BF. Circulating immune complexes in the seronegative spondyloarthropathies. *Clin Immunol Immunopathol* 1982;**22**:384–93.
7. Laurent MR, Panayi GS. Acute-phase proteins and

serum immunoglobulins in ankylosing spondylitis. *Ann Rheum Dis* 1983;**42:**524–8.
8. Vinje O, Moller P, Mellbye J. Immunological variables and acute-phase reactants in patients with ankylosing spondylitis (Bechterew's syndrome) and their relatives. *Clin Rheumatol* 1984;**3:**501–14.
9. Cowling P, Ebringer R, Cawdell D, Ishii M, Ebringer A. C-reactive protein, ESR and Klebsiella in ankylosing spondylitis. *Ann Rheum Dis* 1980;**39:**45–9.
10. Scott DGI, Ring EFJ, Bacon PA. Problems in the assessment of disease activity in ankylosing spondylitis. *Rheumat Rehabil* 1981;**20:**74–80.
11. Calguneris M, Swinburne L, Shinebaum R, Cooke EM, Wright V. Secretory IgA: Immune defence pattern in ankylosing spondylitis and Klebsiella. *Ann Rheum Dis* 1981;**40:**600–4.
12. Hickling P, Turnbull L, Dixon JS. The relationship between disease activity, immunoglobulins and lymphocyte sub-populations in ankylosing spondylitis. *Rheum Rehabil* 1982;**21:**145–50.
13. Sanders KM, Hertzman A, Escobar MR, Littman BH. Correlation of immunoglobulin and C-reactive protein levels in ankylosing spondylitis and rheumatoid arthritis. *Ann Rheum Dis* 1987;**46:**273–6.
14. Collado A, Sanmarti R, Brancos MA *et al*. Correlation of immunoglobulin and C-reactive protein levels in ankylosing spondylitis. *Ann Rheum Dis* 1987;**46:** 719–20.
15. Kendall MJ, Lawrence DS, Shuttleworth GR, Whitfield AGW. Haematology and biochemistry of ankylosing spondylitis. *Br Med J* 1973;**23:**235–7.
16. Dixon JS, Bird HA, Wright V. A comparison of serum biochemistry in ankylosing spondylitis, seronegative and seropositive rheumatoid arthritis. *Ann Rheum Dis* 1981;**40:**404–8.
17. Struthers GR, Lewin IV, Stanworth DR. IgA-alpha$_1$ antitrypsin complexes in ankylosing spondylitis. *Ann Rheum Dis* 1989;**48:**30–4.
18. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. *Arthritis Rheum* 1984;**27:**361–8.
19. Creemers MCW, Franssen MJAM, Putte van de LBA, Gribnau FWJ, Riel van PLCM. Metrotrexate in severe ankylosing spondylitis; an open study. *J Rheumatol* 1995;**22:**1104–7.
20. Schober P. Lendenwirbelsaule und Kreuzschmerzen. *Muench Med Wochenschr* 1937;**84:**336.
21. Adrichem JAM, Korst van der JK. Assessment of the flexibility of the lumbar spine. *Scand J Rheumatol* 1973;**2:**87–91.
22. Domján L, Nemes T, Bálint GP, Tóth Z, Gömör B. A simple method for measuring lateral flexion of the dorsolumbar spine. *J Rheumatol* 1990;**17:**663–5.
23. Mander MM, Simpson JM, McLellan A, Walker D, Goodacre JA, Dick WC. Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. *Ann Rheum Dis* 1987;**46:**197–202.
24. Creemers MCW, van 't Hof MA, Franssen MJAM, Putte van de LBA, Gribnau FWJ, Riel van PLCM. A Dutch version of the functional index for ankylosing spondylitis. Development and validation in a long-term study. *Br J Rheumatol* 1994;**33:**824–6.
25. Dougados M, Gueguen A, Nakache J-P, Nguyen N, Mery C, Amor B. Evaluation of a functional index and an articular index in ankylosing spondylitis. *J Rheumatol* 1988;**15:**302–7.
26. Dougados M, Gueguen A, Nakache J-P, Nguyen N, Mery C, Amor B. Evaluation of a functional index and an articular index in ankylosing spondylitis. *J Rheumatol* 1990;**17:**1254–5.
27. Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrika* 1951;**16:**297–334.
28. van 't Hof MA, Kowalski CJ. In: Prahl Anderson B, Kowalski CH, Heyendaal P, eds. *A mixed longitudinal interdisciplinary study of growth and development*. New York: Academic Press, 1979:161–72, 387–91.
29. Calin A, McShane D, Powers R. Objective measurements in evaluating drug therapy in ankylosing spondylitis. *Curr Ther Res* 1978;**24:**838–42.
30. Franssen MJAM, Gribnau FWJ, Putte van de LBA. Assessment of disease activity in ankylosing spondylitis: the common clinical criteria and an index of disease activity. Thesis. The Netherlands: Catholic University Nijmegen, 1985.
31. Peeters AJ, Wall Bake van den AWL, Albada-Kuipers GA *et al*. IgA containing immune complexes and hematuria in ankylosing spondylitis. A prospective longitudinal study. *J Rheumatol* 1988;**15:**1662–7.
32. Kennedy LG, Edmunds L, Calin A. The natural history of ankylosing spondylitis. Does it burn out? *J Rheumatol* 1993;**20:**688–92.
33. Garrett SL, Kennedy LG, Whitelock HC *et al*. A new approach to defining disease status in AS: the Bath ankylosing spondylitis disease activity index (BASDAI). *Br J Rheumatol* 1993;**32**(suppl. 2):23.
34. Salaffi F, Carotti M, Breceiaroli D, Cervini C. Assessment of ankylosing spondylitis: a first step in the development of a composite index. *Rev Esp Reumatol* 1993;**20**(suppl. 1):489.
35. van de Heijde DMFM, van 't Hof MA, van Riel PLCM *et al*. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990;**49:**916–20.